Transcript for FDA's Media Briefing on the Safe Use of Opioids

Moderator: Karen Riley
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Coordinator: Welcome and thank you for standing by. At this time all participants are in a listen-only mode. During the question and answer session please press star 1 on your touchtone phone. Today's conference is being recorded, if you have any objections you may disconnect at this time.

Now I will turn the meeting over to Miss Karen Riley; ma'am, you may begin.

Karen Riley: Good afternoon and thank you for joining us for today's media briefing related to the safe use of opioids. I'm Karen Riley with FDA's Press Office. With me today is Dr. John Jenkins, Director of the Office of New Drugs, Center for Drug Evaluation and Research at FDA and Dr. Bob Rappaport, Director of the Division of Anesthesia, Analgesia and Rheumatology Products Center for Drug Evaluation and Research FDA.

Dr. Jenkins will provide some opening remarks and then we'll open the phones to some questions. And so Dr. Jenkins, we'll get started. Thank you, Dr. Jenkins.

John Jenkins: All right. Thanks, Karen and good afternoon to those of you on the call and thanks for joining us for today's session. Today I want to tell you about the steps the FDA will be taking over the next several months to address the Agency's continuing concern about unsafe use of narcotic pain relievers. The drugs I'm talking about are both brand name and generic opioid drugs formulated with active ingredients including fentanyl, hydromorphone, methadone, morphine, oxycodone and oxymorphone.

On Friday last week the FDA sent letters to 16 manufacturers of certain opioid drug products indicating that their drugs will be required to have what we call a Risk Evaluation and Mitigation Strategy or REMS. There are 24 products that are affected by these letters and you can find the information about the specific sponsors and products at the link provided on the Web site, which I believe is now live.

A REMS is a strategy to manage a known or potential serious risk associated with a drug or biological product. The FDA has authority to require REMS under Food and Drug Administration Amendments Act of 2007, sometimes referred to as FDAAA, when necessary to ensure that the benefits of a drug outweigh the risk of the product.

Opioid drugs have benefits when used properly and are a necessary component of pain management for certain patients. At the same time opioid drugs have serious risks when used improperly. The FDA, drug manufacturers and others have taken a number of steps in the past to prevent misuse, abuse and accidental overdoses of these drugs including adding additional warnings to the product labeling, implementing risk management plans, conducting interagency collaborations and issuing direct communications to both prescribers and patients.

Despite these efforts the rates of misuse and abuse and of accidental overdoses of opioids have risen over the past decade. The FDA believes that establishing a REMS for opioids will reduce these risks while still ensuring that patients with legitimate need for these drugs will continue to have appropriate access.

The FDA recognizes the need to achieve a balance between appropriate access and risk mitigation and believes an effective strategy would benefit from input from industry, patient advocacy groups, the pain and addiction treatment

communities, the general public and other stakeholders. To that end FDA is planning a series of meetings with stakeholders beginning with the sponsors of the marketed products that are listed in the Web site link that I referred to earlier.

That first meeting with the companies will take place on March 3 and will be designed to discuss the development of the proposed REMS. Additional steps will include discussions with other federal agencies and non-government institutions including patient and consumer advocates, representatives of the pain and addiction treatment communities and other health professionals.

The FDA is also planning a public meeting that we hope to schedule in late spring or early summer to allow for broader public input and participation. Through this process of outreach to stakeholders the FDA hopes to gain valuable information that will inform development of a REMS that will assure access for legitimate patients while limiting unsafe and potentially fatal use of these products.

And with that I'll stop and open up for questions.

Karen Riley: Yes, thank you Dr. Jenkins. Dr. Jenkins referred to a Web page. You can access this most easily by going to the homepage for the Center for Drugs, that's www.fda/cder and look at the What's New - click on What's New which is on the left side of that page and you should be able to find this information for your reference.

Okay Operator we're going to open the call now - open the phone for calls. And before we begin I want to remind everyone that this is for credentialed media only. And when you ask a question you are limited to one question and

one follow-up question and please identify your affiliation when you ask your question. Thank you, Operator.

Coordinator: Thank you. If you'd like to ask a question please press star 1, to withdraw a request press star 2. Once again to ask a question please press star 1. Our first question comes from Daniel DeNoon with WebMD, your line is open.

Daniel DeNoon: Hello. Thank you for taking my question. I'm a little confused - can you tell me what if anything is changing immediately and what changes for consumers you believe will be happening in the near future? Thank you.

John Jenkins: Okay, this is Dr. Jenkins again. Nothing is changing immediately. This will be a process that will play out over the next several months as we engage with the various stakeholders to get input into the design of the REMS program that we will then work with the manufacturers of these products to implement after that time.

So nothing changes immediately. After we get all the input and have the public meeting later this spring or early summer we will take that information back and digest it and then we will let the sponsors know exactly what we'd expect to be included in their REMS. And it will take some time after that for us to work with the companies to get this program up and in place.

This will obviously be a very complex undertaking so it will take some time. So in the short run nothing changes but I think it's important to continue to emphasize to patients and prescribers that they should follow the directions that are in the labeling for these products to try to ensure that they are used for patients who have appropriate indications for use of these products while at the same time trying to limit misuse, abuse and accidental overdoses.

Karen Riley: Thank you. Next question please.

Coordinator: Our next question comes from Lisa Richwine with Reuters; your line is open.

Lisa Richwine: Hi. Thanks for taking my question. And I don't see the information on the Internet which would probably help answer some of my questions. So I'm trying to figure out which makes got these letters. I know it'll be up eventually but were some of the makers - does this apply to companies that have drug applications pending? There's at least two drugs that I know of that are waiting to be approved. And can those drugs not be approved until these REMS are put in place which sounds like it could take many months.

John Jenkins: Well the - you'll see the posting hopefully soon.

Lisa Richwine: Okay.

John Jenkins: The letters went out to companies that have approved applications so these are either approved new drug applications or approved abbreviated new drug applications.

Lisa Richwine: Okay.

John Jenkins: And they're generally for products that have come to be known as either extended release products; some of them are transdermal patches. They're not in general, you know, the more immediate release products although some of the products - the methadone products that are on here are immediate release products.

But you'll see the listing. It's not all opioids...

Lisa Richwine: Okay.

John Jenkins: ...it's certain opioids that we think require the REMS. And I can't comment on any pending applications that are under review.

Lisa Richwine: Okay but these letters did not go - were not directed toward any drugs that are under review?

John Jenkins: The letters only went to manufacturers that have approved applications.

Lisa Richwine: Okay thank you.

Karen Riley: Lisa, this is Karen, I just checked and the page is live.

Lisa Richwine: Okay.

Karen Riley: Let me give you that link again, it's at http://www.fda.gov/cder/drug/infopage/opioids/default.htm.

Lisa Richwine: Okay.

Karen Riley: .../drug/infopage/opioids/default.htm.

(Lisa Richline): Opioids, okay I'll look there. Thanks.

Karen Riley: Sure but it should also be on the What's New. Okay let's take the next question then.

Coordinator: Once again to ask a question please press star 1. Our next question comes from Jennifer Smith with FDA Week; your line is open.

Jennifer Smith: Hi, just a question as to if any of these products, the 24 products that will have to have a REMs, do any of them have RiskMAPs already? And then if opioids are Schedule III drugs and pretty well-restricted, I mean, what really - what's going to be in addition, like what additional measures will the companies likely have to take?

John Jenkins: Right.

Jennifer Smith: I mean what's changed essentially, you know, if they're...

((Crosstalk))

Jennifer Smith: Sure, the first one was about if any of these products had RiskMAPs already in place?

John Jenkins: Yes, as I mentioned several of these products do already have the risk management plans that were put in place in the past before we had the REMS authority. You know, the exact components of the REMS will be something we'll be working out over the course of hearing the public input and then working with the manufacturers.

We will also be working with the Drug Enforcement Administration to work together to ensure that these products are used properly and safely. You know, we believe that there needs to be significant improvements in the education about the safety of these products both for prescribers and for patients. So...

Jennifer Smith: Okay.

John Jenkins: ...those will be components that we will be expecting will be in the REMS. But I think the actual exact details remain to be worked out that's why we're having the stakeholder outreach...

Jennifer Smith: Right.

John Jenkins: ...process to make sure that we develop a program that will meet its goals of not restricting access to legitimate patients while at the same time improving safe use.

Jennifer Smith: I'm sorry, can I just tag onto something that - because it's directly related to what you're saying?

John Jenkins: Okay.

Jennifer Smith: Okay just because - so when it comes to the RiskMAPs -- so they just weren't working? I just want to - I guess I'm just wondering if you're just - if the RiskMAPs might stay the same for the different drugs out there and you're just going to call them REMS instead or will the - do you think there will actually be viable changes whether it comes to labeling language, whether it comes to additional patient monitoring etcetera, that's actually going to change?

John Jenkins: We do not believe that the risk management plans have fully met the goals that we would like to achieve so I think we can expect that the REMS program will go beyond what has been present in the risk management plans.

Jennifer Smith: Okay. Thank you.

Karen Riley: Okay thank you. And I've been told that my Web terminology needs to be brushed up just a little bit; it's not backslash it's a regular forward slash so I do apologize for that. Next question please.

Coordinator: Our next question comes from Matt Perrone with AP; your line is open.

Matt Perrone: Hi thanks guys. I'm wondering if you can just give us any sort of details/color on the scope of this problem? You mentioned that, you know, for a decade the rates of misuse have been increasing; are there any figures you can give us, any specific statistics you can point us to?

John Jenkins: Yeah, I can give you a little bit and then I'll see if Dr. Rappaport wants to add anything. The use of these products is quite extensive. The data we have for 2007 suggested that there were approximately 21 million prescriptions dispensed for the 24 affected products and that represented about 3.7 million unique patients. So this is a very extensively used group of medications.

As far as the risk, it's hard to get exact numbers and to sort out the numbers exactly for the cause of the serious adverse events, but I think it's clear that there are hundreds of deaths reported each year for these products related to misuse which can be intentional or unintentional abuse and accidental overdoses. So, Dr. Rappaport, anything else you'd like to add to that?

Bob Rappaport: Just that the - some data from SAMHSA just came out this morning actually from their national surveys on drug use and health which showed that overall 5.2 million people age 12 years or older reported using prescription pain relievers non-medically in the past month in 2007. And in particular of concern that the numbers seem to be increasing in certain age categories; use among adults age 26 or older increased from 1.3% to 1.6% so this is an ongoing problem that's getting worse.

John Jenkins: And our concerns relate both to the patients that the drugs are prescribed to who may take them inappropriately or maybe even have them prescribed inappropriately as well as others who may gain access to the medications either through, you know, the medicine cabinet at home or these products being sold, you know, by the patients who had them prescribed. So it's for the patients prescribed as well as others who gain access to these drugs.

Matt Perrone: So - but it would be safe to say that the majority of those deaths he talked about resulted from, you know, patients using these inappropriately not necessarily, you know, because of, you know, physicians prescribing them to the wrong patients is what I'm hearing?

John Jenkins: Well I think it's a mixture of all of the above and I think it's going to be hard to sort out which is the most common. There are concerns about physicians prescribing these products to patients who are inappropriate, for example, most of these products are approved for patients with moderate to severe chronic pain who require around the clock opioid treatment. And they need to be opiate tolerant before they receive these because it can be dangerous if you're not used to taking these drugs to be prescribed one of these drugs.

So it's that population of patients; it's also patients not understanding how to take them correctly, maybe chewing the extended release tablets and you get an immediate release of the high dose of opiates that are contained in the tablet. But it's also, you know, family members or other members of the population who get access to these that were, you know, prescribed legitimately, but they make their way into the system and they obviously didn't get any of the warnings about how to use them correctly.

Matt Perrone: I see. Thanks for the call. And Karen if you could just read that address one more time because it's still not on the What's New page.

Karen Riley: Yes we've been - email - deluged with emails about this so here it is, it's http://www.fda.gov/cder/drug/infopage/opioids/default.htm.

John Jenkins: And you might - opioids is spelled OPIOIDS. I know I have trouble remembering how to spell it correctly so you may be typing in the opioids incorrectly.

Karen Riley: Good point. All right, next call please.

Coordinator: Once again to ask a question please press star 1. Our next question comes from Sue Sutter with Scrip World Pharmaceutical News; your line is open.

Sue Sutter: Hi. There was discussion during some advisory committee meetings in November about developing a class-wide REMS across all the opioids; is this what you envision here are single REMS for all of these products?

John Jenkins: Yes.

Sue Sutter: And that's a yes, I'm sorry?

John Jenkins: I'm sorry, go ahead and finish your question.

Sue Sutter: You had also mentioned that there were some opioids I guess that are not included in this list and I was wondering how that would work if there were a class-wide REMS and if you could say what opioids those are that aren't included? Thank you.

John Jenkins: Right. We definitely believe that the best way to affect this REMS will be for it to be the same program for all the affected products. That's one of the reasons that we're leading with the manufacturers of these products on March 3 is to start emphasizing the need to develop one system. In fact the legislation that I referenced, FDAAA, calls for there to be one system for innovators and generics except in rare circumstances.

This obviously is going to be the largest risk management effort we've undertaken, as I said, 21 million prescriptions, so it needs to be a coordinated effort not only among the sponsors but also the pharmacy system and the healthcare system in general and that's why we realize the need to reach out to the stakeholders.

As far as the products that are not being impacted by this REMS, the easy answer is that it's any of the products that are not on the list that we provide on the Web site. Again the characteristic of the products that we are requiring a REMS for are generally products that are extended release, they are products that are transdermal patches like fentanyl transdermal patches; they are methadone products that are used for treating pain, methadone also sometimes being used for treatment of addiction.

The products that are not being requested to have REMS tend to be products that are immediate release products and also another class of fentanyl products are the transmucosal products that are being covered under a separate program. So it's easiest to say what is covered because there are a lot of products in the opiate class that are not being covered because at this time we believe that focusing on the products that are listed will have the most impact on the inappropriate use and the unsafe use.

Karen Riley: Thank you. Next question please.

Coordinator: Our next question comes from Gardiner Harris with the New York Times; your line is open.

Gardiner Harris: Dr. Jenkins, can you give us some sense as to what was the tipping point for this? Was it that you suddenly got this authority? Was it - I mean, obviously this is an issue that's been going on for decades, abuse of these drugs...

John Jenkins: Right.

Gardner Harris: And sort of a technical point is, is fentanyl an opioid? But anyway give us some sense as to what led you to this announcement, A. And, B, how big of a deal is this? I mean to me this sounds like this could fundamentally change the kind of drug disbursal system in the United States if you're talking about bringing in the pharmacies and all the rest. Are we looking at something that is really going to have a substantial impact for cancer patients and others? Is it people are really going to notice this?

John Jenkins: Yeah. Thanks for the question. As far as what led to this, as you're aware and others are aware, we've been concerned about this issue with these products for quite some time. It was the mid-90s when these extended release opioids were first approved by FDA and I guess it's been since around 2000 that we've become aware of very significant problems with misuse, abuse and unintentional overdose.

We've put in place various plans over the years to try to improve the safe use. But I think when we got the new authority under FDAAA we went back and revisited whether there was more that we could do that would be authorized now with our new authority and once we get the interpretation that the new authority would be applicable here if we started working through what type of

program would, we think, would be useful and how we would go about implementing it.

Going to part of your second question, we recognize this is going to be a relatively massive new program because as I said, 21 million prescriptions; that's orders of magnitude greater than the other programs we have in place, now, for example, the isotretinoin program. So we want to do this in a way that achieves the goals.

So yes it's likely that legitimate patients will see new procedures that will be in place for obtaining [these] products, but we hope to make those procedures not so intrusive that it impacts on their ability to receive the products while at the same time meeting the second goal of having an impact on safe use. So we'd like not to impact on legitimate patient access and we would like to be effective in substantially reducing, you know, the deaths and serious adverse events that are being reported because of these products.

And I'll let Dr. Rappaport answer the technical question about whether fentanyl is an opioid.

Bob Rappaport: Yes, fentanyl is definitely an opioid related to sufentanil and remifentanil which are also opioids.

Gardner Harris: One last follow up - and thank you so much for answering those - there has been obviously criminal activity in this also on the part of manufacturers both Purdue Pharma and Cephalon have pleaded guilty to criminally marketing some of these products more widely than they should be. How is it that FDA can ensure that that sort of criminal activity did not lead to death and how would your REMS maybe - are you going to take into account in building

your REMS that some of these manufacturers have and may in the future do these sort of criminal activities?

John Jenkins: Yeah, I would probably separate the REMS program, which is our attempt to try to ensure that, you know, the benefits of the products outweigh their risk under the new authority that Congress provided us in FDAAA from other activities to ensure that sponsors, prescribers and patients are following the law as far as how these products are intended to be marketed and used. You know, these are all controlled substances that are regulated by authority that DEA manages under the Controlled Substances Act.

And I would also say that, you know, FDA will continue to monitor and investigate any, you know, inappropriate marketing of these products. You know, the marketing has to follow the labeling and as part of the REMS program the labeling for these products will likely be changed further and they will also have the REMS program. So I think it's a multi-pronged effort to ensure safe use as well as compliance with all the laws that govern how these products are marketed and dispensed.

Gardner Harris: Thanks.

Karen Riley: Thank you. Next question please.

Coordinator: Our next question comes from Adam Marcus with Pain Medicine News; your line is open.

Adam Marcus: Hi. Thanks for the call. I want to follow up first on the question that was just asked; can you give us some specific examples of how REMS affect marketing for physicians? These products I don't believe are marked to

patients but I also don't believe that Accutane can be marketed to physicians can they?

John Jenkins: Well, these products, as I said, these are generally Schedule II narcotics controlled under the Controlled Substances Act. I believe that that does not prohibit direct-to-consumer advertising of these products, but obviously these products have a more restrictive program already in place that's governed under the Controlled Substances Act. Does that address your question?

Adam Marcus: Well, no, not exactly. If the REMS adds a layer of scrutiny to a label for physician marketing, what is that specifically? I mean the - these products are heavily marketed to physicians but will that have to change?

John Jenkins: Well what we're talking about is putting in place a program to try to ensure that physicians who are prescribing these products are properly trained in their safe use and their appropriate use and that only those physicians are prescribing these products. The details of how to accomplish that are going to need to be worked out through consultation with the various stakeholders. As I mentioned, we are going to be working in partnership with the Drug Enforcement Administration again trying to put in place a program that will affect safe use without unnecessarily restricting access for legitimate patients.

Adam Marcus: Okay and one more question please? There's a substantial difference in the way these products are used outside the hospital and within the hospital. What sort of steps do you think the FDA will have to take to ensure that hospitalized patients who may not be able to have proper consent for example under the Accutane program, for example, are able to get the drug - that it might even be, you know, more reasonable to have more widely in the hospital?

John Jenkins: Well again our focus is going to be making sure that the prescribers are educated and understand the risk associated with these products and the appropriate patient population that should receive these products.

Just as an example, we continue to see reports of patients who do not have chronic pain, who have an acute self-limiting condition, who are receiving these extended release or transdermal products that are not opiate-tolerant and they're getting into trouble; and some of them are dying. We need to make sure that prescribers are making, you know, well informed decisions whether it be for an inpatient or an outpatient use of the product.

And also we want to make sure that the patients themselves are educated about the risk of these products and how to use them correctly and, you know, how to destroy them if they have extras that they don't need at the end of their prescription; all those factors to try to protect the patient who was the legitimate patient who received the prescription and also to try to avoid the product becoming available to family members or others in the community who may not understand how to use them safely.

Adam Marcus: Thank you.

Karen Riley: Thank you. We have time for two more questions. And before we take those last two questions I want to announce that we are now live on What's New from CDER so that will certainly save on the clicking. Okay Operator let's take the next caller.

Coordinator: Our next question comes from Rita Rubin with USA Today; your line is open.

Rita Rubin: Thanks for taking my question. Are the programs in place for isotretinoid and for thalidomide, are those REMS or, you know, can you give me example of maybe what the biggest REMS program so far as have been?

John Jenkins: Right. The programs for isotretinoid and thalidomide were put in place before FDAAA so they were initially risk management plans but we published a notice in the Federal Register last spring where we determined that those programs are deemed to be REMS. And the companies were required to submit their programs to convert those to REMS by September of 2008. All of those deemed REMS programs have been submitted and are being reviewed.

While we're going through that process the existing programs remain in place. Since we gained the authority in March of 2008 I think we have approved four new REMS programs with elements to assure safe use and one of the ones that I recall was Entereg which is a product used in the hospital after a patient had abdominal surgery so there's only been four new ones.

The largest restricted program is probably the isotretinoin program that's been in place now for a few years and that's a deemed REMS but it was retroactively converted into a REMS and that submission is still under review.

Adam Marcus: Okay, I'm sorry, could you spell the drug that you mentioned used after abdominal surgery?

John Jenkins: E N T E R E G,. I, believe, Entereg.

Adam Marcus: Okay, thank you.

Karen Riley: Thank you.

Coordinator: Our next question comes from Bridget Kuehn with JAMA Medical News; your line is open.

Bridget Kuehn: Hi. I was wondering if you had data that these extended release formulas are causing more deaths. And if you are also going to look into the immediate release formulations since it seems like those would be more readily available to more people?

John Jenkins: Right. Well yes we have seen, you know, data and adverse event reports to lead us to be concerned about these extended release and high potency formulations. There's no doubt that the products that are not covered by this proposal can be dangerous if misused or abused as well. We're focusing our attention on these products because they generally contain very high doses of the product or if they don't contain a high dose they can be - their extended release mechanism can be defeated so that all of the dose that was intended for a 12 or 24-hour period can be released quickly and can cause patients to get into trouble.

So we're focusing on these because these are the ones that seem to be causing the majority of the problems we're seeing with serious adverse reactions and death and they need to be, you know, used very carefully. I gave the example earlier of patients needing to be those with moderate to severe chronic pain who require around the clock opiate therapy. We continue to see case reports where someone with a sprained ankle is given a fentanyl or an extended release oxycodone tablet. They're not opiate-tolerant; they don't have chronic pain and they get into trouble and could suffer a serious adverse reaction.

So we're focusing on these because these require the most training and understanding to use them safely.

Bridget Kuehn: Thank you.

Karen Riley: Thank you very much for participating in today's call. A replay of the briefing will be available one hour after the event ends and you have that information in your media advisory. And if you have any additional questions you can email me or call me and that's on your media advisory too. Thank you very much.

John Jenkins: Thank you.

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